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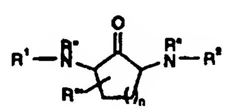
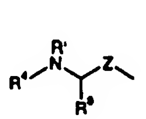
(54) Title: INHIBITORS OF CYSTEINE PROTEASE

(57) Abstract

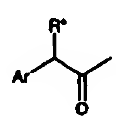
This invention relates to compounds of formula (I), wherein R^1 is (i), (ii), (iii), or (iv); R^2 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^5C(O)$-, $R^5C(S)$-, R^5SO_2-, $R^5OC(O)$-, $R^5R'NC(O)$-, $R^5R'NC(S)$-, adamantyl-C(O)- or (v); each R" independently is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl; R''' is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl; each R^3 independently is H, C_{2-6}alkenyl, C_{2-6}alkynyl, Het, Ar or C_{1-6}alkyl optionally substituted by OR', SR', NR'_2, $R'NC(O)OR^5$, CO_2R', $CO_2NR'_2$, N(C=NH)NH_2, Het or Ar; R^4 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^5C(O)$-, $R^5C(S)$-, R^5SO_2-, $R^5OC(O)$-, $R^5R'NC(O)$-, $R^5R'NC(S)$-, R'HNCH(R')C(O)-, or $R^5OC(O)NR'CH(R')C(O)$-; each R^5 independently is C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, Ar-C_{0-6}alkoxy, Het-C_{0-6}alkoxy, or C_{1-6}alkyl optionally substituted by OR', SR', NR'_2, $R'NC(O)OR^5$, CO_2R', $CO_2NR'_2$, N(C=NH)NH_2, Het or Ar; R^6 is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl or Het-C_{0-6}alkyl and R^7 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^5C(O)$-, $R^5C(S)$-, R^5SO_2-, $R^5OC(O)$-, $R^5R'NC(O)$-, $R^5R'NC(S)$-, R'HNCH(R')C(O)- or $R^5OC(O)NR'CH(R')C(O)$-; or R^6 and R^7 are connected to form a pyrrolidine, a piperidine, or a morpholine ring; each R' independently is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl; R* is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl; Y is a single bond or O; each Z independently is CO or CH_2; and n is 1, 2, or 3; or a pharmaceutically acceptable salt thereof, which are inhibitors of cysteine proteases, particularly cathepsin K, and are useful in the treatment of diseases in which inhibition of bone loss is a factor.



(I)



(i)



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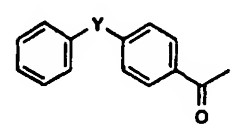

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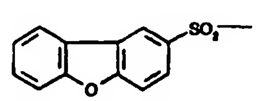

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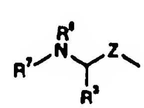

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INHIBITORS OF CYSTEINE PROTEASE

Field of the Invention

This invention relates to novel protease inhibitors, particularly inhibitors of cysteine and serine proteases, more particularly compounds which inhibit cysteine proteases, even more particularly compounds which inhibit cysteine proteases of the papain superfamily, yet more particularly compounds which inhibit cysteine proteases of the cathepsin family, most particularly compounds which inhibit cathepsin K. Such compounds are particularly useful for treating diseases in which cysteine proteases are implicated, especially diseases of excessive bone or cartilage loss, e.g., osteoporosis, periodontitis, and arthritis.

Background of the Invention

Cathepsin K is a member of the family of enzymes which are part of the papain superfamily of cysteine proteases. Cathepsins B, H, L, N and S have been described in the literature. Recently, cathepsin K polypeptide and the cDNA encoding such polypeptide were disclosed in U.S. Patent No. 5,501,969 (called cathepsin O therein). Cathepsin K has been recently expressed, purified, and characterized. Bossard, M. J., et al., (1996) *J. Biol. Chem.* **271**, 12517-12524; Drake, F.H., et al., (1996) *J. Biol. Chem.* **271**, 12511-12516; Bromme, D., et al., (1996) *J. Biol. Chem.* **271**, 2126-2132.

Cathepsin K has been variously denoted as cathepsin O, cathepsin X or cathepsin O2 in the literature. The designation cathepsin K is considered to be the more appropriate one (name assigned by Nomenclature Committee of the International Union of Biochemistry and Molecular Biology).

Cathepsins of the papain superfamily of cysteine proteases function in the normal physiological process of protein degradation in animals, including humans, e.g., in the degradation of connective tissue. However, elevated levels of these enzymes in the body can result in pathological conditions leading to disease. Thus, cathepsins have been implicated in various disease states, including but not limited to, infections by pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei brucei, and Crithidia fusiculata; as well as in schistosomiasis malaria, tumor metastasis, metachromatic leukodystrophy, muscular dystrophy, amytrophy, and the like. *See* International Publication Number WO 94/04172, published on March 3, 1994, and references cited therein. *See also* European Patent Application EP 0 603 873 A1, and references cited therein. Two bacterial cysteine

proteases from P. gingivallis, called gingipains, have been implicated in the pathogenesis of gingivitis. Potempa, J., et al. (1994) *Perspectives in Drug Discovery and Design*, 2, 445-458.

Cathepsin K is believed to play a causative role in diseases of excessive bone or cartilage loss. Bone is composed of a protein matrix in which spindle- or plate-shaped crystals of hydroxyapatite are incorporated. Type I Collagen represents the major structural protein of bone comprising approximately 90% of the structural protein. The remaining 10% of matrix is composed of a number of non-collagenous proteins, including osteocalcin, proteoglycans, osteopontin, osteonectin, thrombospondin, fibronectin, and bone sialoprotein. Skeletal bone undergoes remodeling at discrete foci throughout life. These foci, or remodeling units, undergo a cycle consisting of a bone resorption phase followed by a phase of bone replacement.

Bone resorption is carried out by osteoclasts, which are multinuclear cells of hematopoietic lineage. The osteoclasts adhere to the bone surface and form a tight sealing zone, followed by extensive membrane ruffling on their apical (i.e., resorbing) surface. This creates an enclosed extracellular compartment on the bone surface that is acidified by proton pumps in the ruffled membrane, and into which the osteoclast secretes proteolytic enzymes. The low pH of the compartment dissolves hydroxyapatite crystals at the bone surface, while the proteolytic enzymes digest the protein matrix. In this way, a resorption lacuna, or pit, is formed. At the end of this phase of the cycle, osteoblasts lay down a new protein matrix that is subsequently mineralized. In several disease states, such as osteoporosis and Paget's disease, the normal balance between bone resorption and formation is disrupted, and there is a net loss of bone at each cycle. Ultimately, this leads to weakening of the bone and may result in increased fracture risk with minimal trauma.

The abundant selective expression of cathepsin K in osteoclasts strongly suggests that this enzyme is essential for bone resorption. Thus, selective inhibition of cathepsin K may provide an effective treatment for diseases of excessive bone loss, including, but not limited to, osteoporosis, gingival diseases such as gingivitis and periodontitis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease. Cathepsin K levels have also been demonstrated to be elevated in chondroclasts of osteoarthritic synovium. Thus, selective inhibition of cathepsin K may also be useful for treating diseases of excessive cartilage or matrix degradation, including, but not limited to, osteoarthritis and rheumatoid arthritis. Metastatic neoplastic cells also typically express high levels of proteolytic enzymes that degrade the surrounding matrix. Thus, selective inhibition of cathepsin K may also be useful for treating certain neoplastic diseases.

It now has been discovered that a novel class of compounds are protease inhibitors, most particularly inhibitors of cathepsin K, and these compounds are useful for treating

diseases in which inhibition of bone resorption is indicated, such as osteoporosis and periodontal disease.

Summary of the Invention

An object of the present invention is to provide protease inhibitors, particularly such inhibitors of cysteine and serine proteases, more particularly such compounds which inhibit cysteine proteases, even more particularly such compounds which inhibit cysteine proteases of the papain superfamily, yet more particularly such compounds which inhibit cysteine proteases of the cathepsin family, most particularly such compounds which inhibit cathepsin K, and which are useful for treating diseases which may be therapeutically modified by altering the activity of such proteases.

Accordingly, in the first aspect, this invention provides a compound according to formula (I).

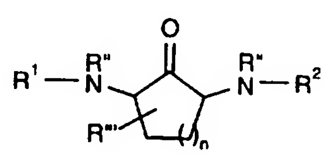
In another aspect, this invention provides a pharmaceutical composition comprising a compound according to formula (I) and a pharmaceutically acceptable carrier.

In yet another aspect, this invention provides a method of treating diseases in which the disease pathology may be therapeutically modified by inhibiting proteases, particularly cysteine and serine proteases, more particularly cysteine proteases, even more particularly cysteine proteases of the papain superfamily, yet more particularly cysteine proteases of the cathepsin family, most particularly cathepsin K.

In a particular aspect, the compounds of this invention are especially useful for treating diseases characterized by bone loss, such as osteoporosis and gingival diseases, such as gingivitis and periodontitis, or by excessive cartilage or matrix degradation, such as osteoarthritis and rheumatoid arthritis.

Detailed Description of the Invention

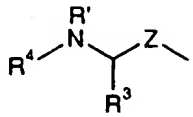
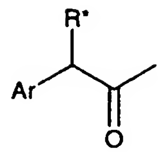
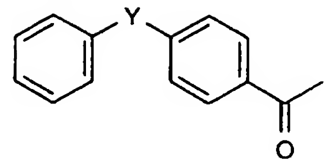
The present invention provides compounds of formula (I):

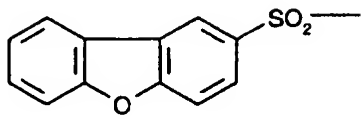


(I)

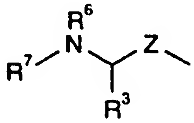
wherein:

R^1 is

 ,  ,  , or

 ;

R^2 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^5C(O)$-, $R^5C(S)$-, R^5SO_2-, $R^5OC(O)$-, $R^5R'NC(O)$-, $R^5R'NC(S)$-, adamantyl-C(O)-, or

 ;

each R" independently is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R"' is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

each R^3 independently is H, C_{2-6}alkenyl, C_{2-6}alkynyl, Het, Ar or C_{1-6}alkyl optionally substituted by OR', SR', NR'_2, $R'NC(O)OR^5$, CO_2R', $CO_2NR'_2$, $N(C{=}NH)NH_2$, Het or Ar;

R^4 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^5C(O)$-, $R^5C(S)$-, R^5SO_2-, $R^5OC(O)$-, $R^5R'NC(O)$-, $R^5R'NC(S)$-, R'HNCH(R')C(O)-, or $R^5OC(O)NR'CH(R')C(O)$-;

each R^5 independently is C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, Ar-C_{0-6}alkoxy, Het-C_{0-6}alkoxy, or C_{1-6}alkyl optionally substituted by OR', SR', NR'_2, $R'NC(O)OR^5$, CO_2R', $CO_2NR'_2$, $N(C{=}NH)NH_2$, Het or Ar;

R^6 is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl and R^7 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^5C(O)$-, $R^5C(S)$-, R^5SO_2-, $R^5OC(O)$-, $R^5R'NC(O)$-, $R^5R'NC(S)$-, R'HNCH(R')C(O)-, or $R^5OC(O)NR'CH(R')C(O)$-; or R^6 and R^7 are connected to form a pyrrolidine, a piperidine, or a morpholine ring;

each R' independently is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R* is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

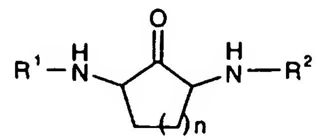
Y is a single bond or O;

each Z independently is CO or CH_2; and

n is 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.

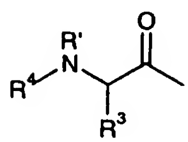
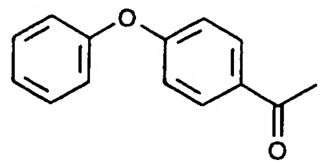
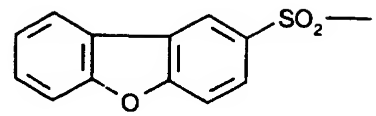
Preferably, the present invention provides compounds of formula (Ia):



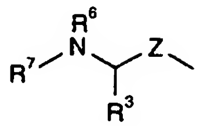
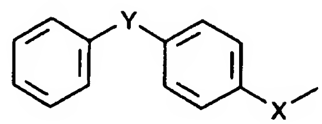
(Ia)

wherein:

R^1 is

, , or ;

R^2 is

 or ;

X is CO, SO_2, or CH_2-CO;

Y is a single bond or O;

Z is CO or CH_2;

each R^3 independently is C_{4-6}alkyl, C_{4-6}alkenyl, or benzyl;

R^4 is C_{1-6}alkyl, Ar-C_{0-6}alkyl, R^5CO-, R^5SO_2- R^5OC(O)-, or R^5NHCO;

R' is H or C_{1-4}alkyl;

R^6 is H or C_{1-4}alkyl;

R^7 is C_{1-6}alkyl, Ar-C_{0-6}alkyl, R^5CO-, R^5SO_2- R^5OC(O)-, or R^5NHCO;

each R^5 independently is Ar-C_{0-6}alkyl or Het-C_{0-6}alkyl; and

n is 1 or 2;

or a pharmaceutically acceptable salt thereof.

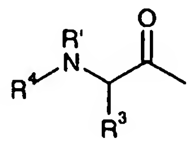
Also included in this invention are hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are considered to be any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo*. In cases wherein the compounds of this invention may have one or more chiral centers, unless specified, this invention includes each unique nonracemic compound which may be synthesized and resolved by conventional techniques. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is

contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

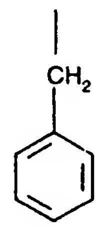
The meaning of any substituent at any one occurrence in formula (I) or any subformula thereof is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

With respect to formula (Ia):

Suitably R^1 is



in which R^4 is $R^5OC(O)$- and R^5 is preferably



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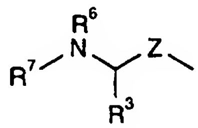
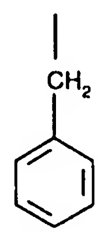
Suitably R^2 is



, in which Z is CO, R^7 is $R^5OC(O)$- and R^5 is preferably



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Suitably R' and R^6 are each H and each R^3 is i-butyl.

Specific representative compounds of this invention are:

trans-N,N'-bis-(benzyloxycarbonyl-L-leucinyl)-1-3-diamino-cyclopentanone and

trans-N,N'-bis-(benzyloxycarbonyl-L-leucinyl)-1-3-diamino-cyclohexanone;

or a pharmaceutically acceptable salt thereof.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of this invention. In general, the amino acid

abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in *Eur. J. Biochem.*, 158, 9 (1984). The term amino acid as used herein refers to the D- or L- isomers of alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine.

C_{1-4}alkyl as applied herein is meant to include substituted and unsubstituted methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and t-butyl groups. C_{1-6}alkyl additionally includes substituted or unsubstituted pentyl, n-pentyl, isopentyl, neopentyl and hexyl and the simple aliphatic isomers thereof. Any C_{1-4}alkyl or C_{1-6}alkyl group may be optionally substituted by one to three groups selected from OR', $N(R')_2$, SR', CF_3, NO_2, CN, CO_2R', and CON(R'), unless otherwise indicated. C_{0-4}alkyl and C_{0-6}alkyl additionally indicates that no alkyl group need be present (*e.g.*, that a covalent bond is present).

C_{3-6}cycloalkyl as applied herein is meant to include substituted and unsubstituted cyclopropane, cyclobutane, cyclopentane, and cyclohexane.

C_{2-6}alkenyl as applied herein means an alkyl group of 2 to 6 carbons wherein a carbon-carbon single bond is replaced by a carbon-carbon double bond. C_{2-6}alkenyl includes ethylene, 1-propene, 2-propene, 1-butene, 2-butene, isobutene and the several isomeric pentenes and hexenes. Both cis and trans isomers are included.

"C_{2-6}alkynyl" means an alkyl group of 2 to 6 carbons wherein one carbon-carbon single bond is replaced by a carbon-carbon triple bond. C_{2-6} alkynyl includes acetylene, 1-propyne, 2-propyne, 1-butyne, 2-butyne, 3-butyne and the simple isomers of pentyne and hexyne.

"Halogen" or "halo" means F, Cl, Br, and I.

"Ar" or "aryl" means unsubstituted phenyl or naphthyl; or phenyl or naphthyl substituted by one or more of Ph-C_{0-6}alkyl, Het-C_{0-6}alkyl, C_{1-6}alkoxy, Ph-C_{0-6}alkoxy, Het-C_{0-6}alkoxy, OH, $(CH_2)_{1-6}NR'R'$, $O(CH_2)_{1-6}NR'R'$; wherein each R' independently is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl; or phenyl or naphthyl substituted by one to three moieties selected from C_{1-4}alkyl, OR', $N(R')_2$, SR', CF_3, NO_2, CN, CO_2R', CON(R'), F, Cl, Br and I, or substituted by a methylenedioxy group.

As used herein "Het" or "heterocyclic" represents a stable 5- to 7-membered monocyclic or a stable 7- to 10-membered bicyclic heterocyclic ring, which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure, and may

optionally be substituted with one or two moieties selected from C_{1-4}alkyl, OR', $N(R')_2$, SR', CF_3, NO_2, CN, CO_2R', CON(R'), F, Cl, Br and I, where R' is as defined hereinbefore. Examples of such heterocycles include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, pyridyl, pyrazinyl, oxazolidinyl, oxazolinyl, oxazolyl, isoxazolyl, morpholinyl, thiazolidinyl, thiazolinyl, thiazolyl, quinuclidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, benzoxazolyl, furyl, pyranyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzoxazolyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, oxadiazolyl, benzothiazolyl, benzoisothiazolyl, benzisoxazolyl, pyrimidinyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,5-napthyridinyl, 1,6-napthyridinyl, 1,7-napthyridinyl, 1,8-napthyridinyl, tetrazolyl, 1,2,3-triazolyl, and 1,2,4-triazolyl.

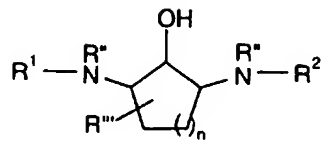
"HetAr" or "heteroaryl" means any heterocyclic moiety encompassed by the above definition of Het which is aromatic in character, e.g., pyridinyl, quinolinyl, isoquinolinyl, pyrrolyl, pyrazolyl, imidazolyl, pyridyl, pyrazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl, furyl, thienyl, benzoxazolyl, oxadiazolyl, benzothiazolyl, benzoisothiazolyl, benzisoxazolyl, pyrimidinyl, cinnolinyl, quinazolinyl, quinoxalinyl, 1,5-napthyridinyl, 1,6- napthyridinyl, 1,7- napthyridinyl, 1,8- napthyridinyl, tetrazolyl, 1,2,3-triazolyl, and 1,2,4-triazolyl.

Certain radical groups are abbreviated herein. t-Bu refers to the tertiary butyl radical, Boc refers to the t-butyloxycarbonyl radical, Fmoc refers to the fluorenylmethoxycarbonyl radical, Ph refers to the phenyl radical, Cbz refers to the benzyloxycarbonyl radical.

Certain reagents are abbreviated herein. DCC refers to dicyclohexylcarbodiimide, DMAP is 2,6-dimethylaminopyridine, EDC refers to N-ethyl-N'(dimethylaminopropyl)-carbodiimide. HOBt refers to 1-hydroxybenzotriazole, DMF refers to dimethyl formamide, BOP refers to benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate, DMAP is dimethylaminopyridine, Lawesson's reagent is 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide, NMM is N-methylmorpholine, TFA refers to trifluoroacetic acid, TFAA refers to trifluoroacetic anhydride and THF refers to tetrahydrofuran.

The compounds of formula (I) are generally prepared using a process which comprises:

reacting a compound of the formual (II):



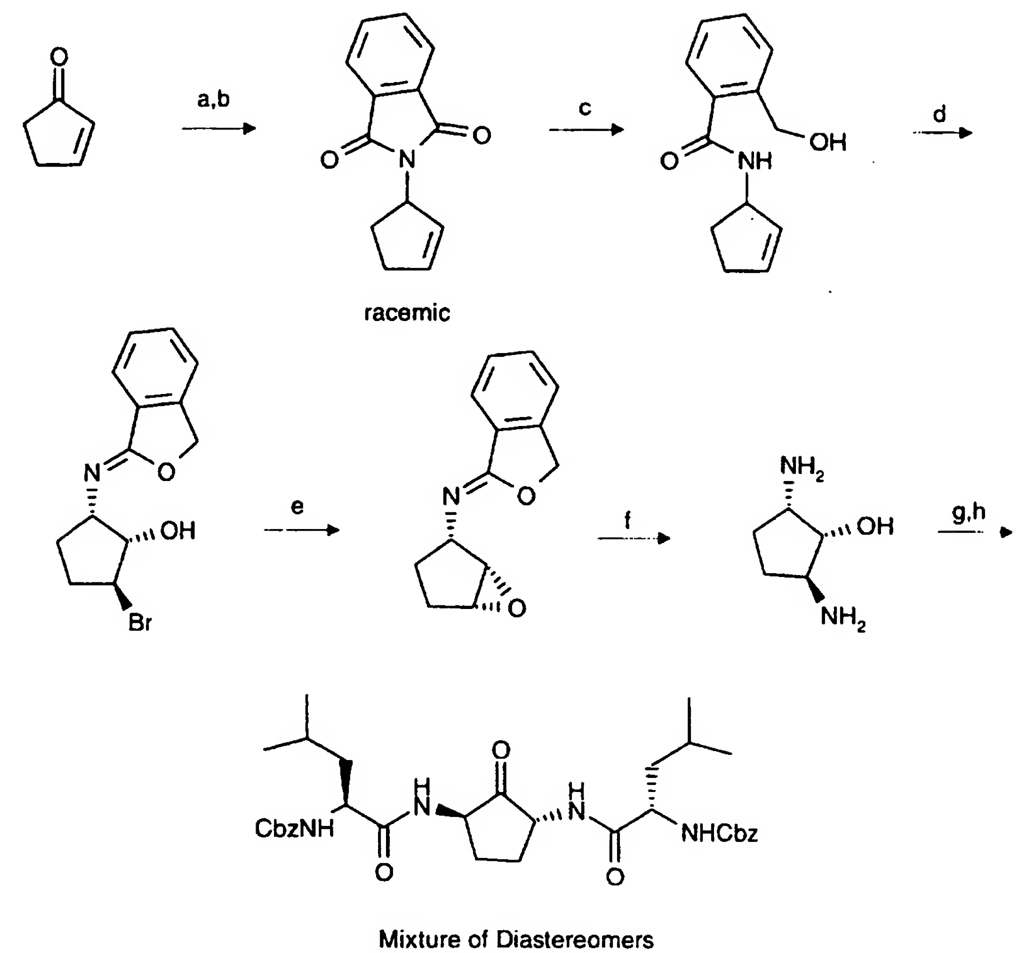
(II)

wherein R^1, R^2, R", R"' and n are as defined in formula (I), with any reactive functional groups protected, with an oxidizing agent;

and thereafter removing any protecting groups and optionally forming a pharmaceutically acceptable salt.

Compounds of the formula I wherein n is 1 are prepared by methods analogous to those described in Scheme 1.

Scheme 1

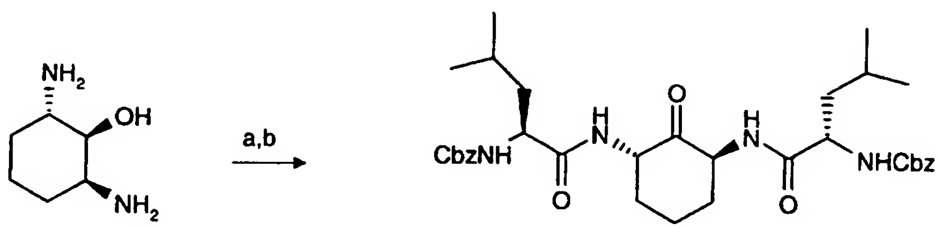


a: LAH; b: triphenylphosphine, DEAD, phthalimide; c: $NaBH_4$; d: NBS; e: KOH; f: NH_3; g: Cbz-Leu-OH, EDCI, HOBT; h: Jones

According to Scheme 1, cyclopentene-2-ol (as described in Brown, H. C.; Hess, H.M. *J. Org. Chem.* **1969**, *34*, 2206) was converted to a its phthalimide by Mitsunobu reaction. Reduction of the phthalimide with sodium borohydride, followed by bromination of the alkene with N-bromosuccinimide provided the *N*-(1(3*H*)-isobenzofuranylidene)- 1-bromo-2-hydroxy-cyclopentyl-3-amine synthetic intermediate, which was converted into its epoxide with potassium hydroxide. Treatment of the epoxide with ammonia in a bomb provided trans-1,3-diamino cyclopentanol, which was acylated with Cbz-leucine/ HBTU and oxidized to provide the desired trans-N,N'-bis-(benzyloxycarbonyl-L-leucinyl)-1-3-diamino-cyclopentanone.

Compounds of the formula I wherein n is 2 are prepared by methods analogous to those described in Scheme 2.

Scheme 2



racemic

Mixture of Diastereomers

a: Cbz-Leu-OH, EDCI, HOBT; b: Jones

According to Scheme 2, the known 1,3-diamino-cyclopentanol (as described by Sammes, P.G.; Phetford, D. *J. Chem. Soc. Perkin Trans. I*, **1989**, 655) was acylated with Cbz-leucine/ HBTU and oxidized to provide the desired trans-N,N'-bis-(benzyloxycarbonyl-L-leucinyl)-1-3-diamino-cyclohexanone.

The starting materials used herein are commercially available amino acids or prepared by routine methods well known in the art as can be found in standard reference books, such as the COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. I-VI (published by Wiley-Interscience).

Coupling methods to form amide bonds herein are generally well known to the art. The methods of peptide synthesis generally set forth by Bodansky *et al.*, THE PRACTICE OF PEPTIDE SYNTHESIS, Springer-Verlag, Berlin, 1984; E. Gross and J. Meienhofer, THE PEPTIDES, Vol. 1, 1-284 (1979); and J.M. Stewart and J.D. Young, SOLID PHASE PEPTIDE SYNTHESIS, 2d Ed., Pierce Chemical Co., Rockford, Ill., 1984. are generally illustrative of the technique and are incorporated herein by reference.

Synthetic methods to prepare the compounds of this invention frequently employ protective groups to mask a reactive functionality or minimize unwanted side reactions. Such protective groups are described generally in Green, T.W, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, John Wiley & Sons, New York (1981). Amino protecting groups generally refers to the Boc, acetyl, benzoyl, Fmoc and Cbz groups and derivatives thereof as known to the art. Methods for protection and deprotection, and replacement of an amino protecting group with another moiety are well known.

Acid addition salts of the compounds of formula (I) are prepared in a standard manner in a suitable solvent from the parent compound and an excess of an acid, such as hydrochloric, hydrobromic, hydrofluoric, sulfuric, phosphoric, acetic, trifluoroacetic, maleic, succinic or methanesulfonic. Certain of the compounds form inner salts or zwitterions which may be acceptable. Cationic salts are prepared by treating the parent compound with an excess of an alkaline reagent, such as a hydroxide, carbonate or alkoxide, containing the appropriate cation; or with an appropriate organic amine. Cations such as Li^+, Na^+, K^+, Ca^{++}, Mg^{++} and NH_4^+ are specific examples of cations present in pharmaceutically acceptable salts. Halides, sulfate, phosphate, alkanoates (such as acetate and trifluoroacetate), benzoates, and sulfonates (such as mesylate) are examples of anions present in pharmaceutically acceptable salts.

This invention also provides a pharmaceutical composition which comprises a compound according to formula (I) and a pharmaceutically acceptable carrier. Accordingly, the compounds of formula (I) may be used in the manufacture of a medicament. Pharmaceutical compositions of the compounds of formula (I) prepared as hereinbefore described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, these compounds may be encapsulated, tableted or prepared in a emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Liquid carriers include syrup, peanut oil, olive oil, saline and water. The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing, when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a

syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, the compounds of this invention may also be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository.

The compounds of formula (I) are useful as protease inhibitors, particularly as inhibitors of cysteine and serine proteases, more particularly as inhibitors of cysteine proteases, even more particularly as inhibitors of cysteine proteases of the papain superfamily, yet more particularly as inhibitors of cysteine proteases of the cathepsin family, most particularly as inhibitors of cathepsin K. The present invention also provides useful compositions and formulations of said compounds, including pharmaceutical compositions and formulations of said compounds.

The present compounds are useful for treating diseases in which cysteine proteases are implicated, including infections by pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei, and Crithidia fusiculata; as well as in schistosomiasis, malaria, tumor metastasis, metachromatic leukodystrophy, muscular dystrophy, amytrophy; and especially diseases in which cathepsin K is implicated, most particularly diseases of excessive bone or cartilage loss, including osteoporosis, gingival disease including gingivitis and periodontitis, arthritis, more specifically, osteoarthritis and rheumatoid arthritis, Paget's disease; hypercalcemia of malignancy, and metabolic bone disease.

Metastatic neoplastic cells also typically express high levels of proteolytic enzymes that degrade the surrounding matrix, and certain tumors and metastatic neoplasias may be effectively treated with the compounds of this invention.

The present invention also provides methods of treatment of diseases caused by pathological levels of proteases, particularly cysteine and serine proteases, more particularly cysteine proteases, even more particularly as inhibitors of cysteine proteases of the papain superfamily, yet more particularly cysteine proteases of the cathepsin family, which methods comprise administering to an animal, particularly a mammal, most particularly a human in need thereof a compound of the present invention. The present invention especially provides methods of treatment of diseases caused by pathological levels of cathepsin K, which methods comprise administering to an animal, particularly a mammal, most particularly a human in need thereof an inhibitor of cathepsin K, including a compound of the present invention. The present invention particularly provides methods for treating diseases in which cysteine proteases are implicated, including infections by pneumocystis carinii, trypsanoma cruzi, trypsanoma brucei, and Crithidia fusiculata; as well as in schistosomiasis, malaria, tumor metastasis, metachromatic leukodystrophy, muscular dystrophy, amytrophy, and especially diseases in which cathepsin K is implicated,

most particularly diseases of excessive bone or cartilage loss, including osteoporosis, gingival disease including gingivitis and periodontitis, arthritis, more specifically, osteoarthritis and rheumatoid arthritis, Paget's disease, hypercalcemia of malignancy, and metabolic bone disease.

This invention further provides a method for treating osteoporosis or inhibiting bone loss which comprises internal administration of a compound of formula (I) and other inhibitors of bone resorption, such as bisphosphonates (i.e., allendronate), hormone replacement therapy, anti-estrogens, or calcitonin. In addition, treatment with a compound of this invention and an anabolic agent, such as bone morphogenic protein, iproflavone, may be used to prevent bone loss and/or to increase bone mass.

For acute therapy, parenteral administration of a compound of formula (I) is preferred. An intravenous infusion of the compound in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the parenteral dose will be about 0.01 to about 100 mg/kg; preferably between 0.1 and 20 mg/kg, in a manner to maintain the concentration of drug in the plasma at a concentration effective to inhibit cathepsin K. The compounds are administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 400 mg/kg/day. The precise level and method by which the compounds are administered is readily determined by one routinely skilled in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

The compounds of this invention may also be administered orally to the patient, in a manner such that the concentration of drug is sufficient to inhibit bone resorption other such indication as disclosed herein. Typically, a pharmaceutical composition containing the compound is administered at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.5 to about 20 mg/kg.

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

The compounds of this invention may be tested in one of several biological assays to determine the concentration of compound which is required to have a given pharmacological effect.

Determination of cathepsin K proteolytic catalytic activity:

All assays for cathepsin K were carried out with human recombinant enzyme derived from osteoclastoma cells. Procedures for obtaining such enzyme, such as those disclosed by Inaoka, *et al.*, *Biochem. Biophys. Res. Commun.*, **1995**, *206*, 89; Shi, *et al.*,

FEBS Lett., **1995**, *357*, 129; and Brömme, *et al.*, *Biol. Chem. Hoppe-Seyler*, **1995**, 376, 379, are known in the art. Standard assay conditions for the determination of kinetic constants used a fluorogenic peptide substrate, typically Cbz-Phe-Arg-AMC, and were determined in 100 mM Na acetate at pH 5.5 containing 20 mM cysteine and 5 mM EDTA. Stock substrate solutions were prepared at concentrations of 10 or 20 mM in DMSO with 20 uM final substrate concentration in the assays. All assays contained 10% DMSO. Independent experiments found that this level of DMSO had no effect on enzyme activity or kinetic constants. All assays were conducted at ambient temperature. Product fluorescence (excitation at 360 nM; emission at 460 nM) was monitored with a Perceptive Biosystems Cytofluor II fluorescent plate reader. Product progress curves were generated over 20 to 30 min following formation of AMC product.

Inhibition of Cathepsin K Activity:

Potential inhibitors were evaluated using the progress curve method. Assays were carried out in the presence of variable concentrations of test compound. Reactions were initiated by addition of enzyme to buffered solutions of inhibitor and substrate. Data analysis was conducted according to one of two procedures depending on the appearance of the progress curves in the presence of inhibitors. For those compounds whose progress curves were linear, apparent inhibition constants ($K_{i,app}$) were calculated according to equation 1 (Brandt *et al.*, *Biochemitsry*, **1989**, *28*, 140):

$$v = V_m A / [K_a(1 + I/K_{i,\ app}) + A] \qquad (1)$$

where v is the velocity of the reaction with maximal velocity V_m , A is the concentration of substrate with Michaelis constant of K_a, and I is the concentration of inhibitor.

For those compounds whose progress curves showed downward curvature characteristic of time-dependent inhibition, the data from individual sets was analyzed to give k_{obs} according to equation 2:

$$[\mathrm{AMC}] = v_{ss}\, t + (v_0 - v_{ss})\, [1 - \exp(-k_{obs}t)] / k_{obs} \qquad (2)$$

where [AMC] is the concentration of product formed over time t, v_0 is the initial reaction velocity and v_{ss} is the final steady state rate. Values for k_{obs} were then analyzed as a linear function of inhibitor concentration to generate an apparent second order rate constant (k_{obs} / inhibitor concentration or k_{obs} / [I]) describing the time-dependent inhibition. A complete discussion of this kinetic treatment has been fully described (Morrison *et al.*, *Adv. Enzymol. Relat. Areas Mol. Biol.*, **1988**, *61*, 201).

Compounds of the present invention inhibit the human cathepsin K enzyme with a K_i in the concentration range of about 15 micromolar, where competitive kinetics are observed. Compounds which show non-linear kinetics show a k_{obs} of about 56/(M x sec).

Compounds of this invention are also tested for *in vitro* and *in vivo* bone resorption in assays standard in the art for evaluating inhibition of bone formation, such as the pit formation assay disclosed in EP 528 587, which may also be performed using human osteoclasts in place of rat osteoclasts, according to the following procedure:

Human Osteoclast Resorption Assay

Aliquots of osteoclastoma-derived cell suspensions were removed from liquid nitrogen storage, warmed rapidly at 37°C and washed x1 in RPMI-1640 medium by centrifugation (1000 rpm, 5 min at 4°C). The medium was aspirated and replaced with murine anti-HLA-DR antibody, diluted 1:3 in RPMI-1640 medium, and incubated for 30 min on ice The cell suspension was mixed frequently.

The cells were washed x2 with cold RPMI-1640 by centrifugation (1000 rpm, 5 min at 4°C) and then transferred to a sterile 15 mL centrifuge tube. The number of mononuclear cells were enumerated in an improved Neubauer counting chamber.

Sufficient magnetic beads (5 / mononuclear cell), coated with goat anti-mouse IgG, were removed from their stock bottle and placed into 5 mL of fresh medium (this washes away the toxic azide preservative). The medium was removed by immobilizing the beads on a magnet and is replaced with fresh medium.

The beads were mixed with the cells and the suspension was incubated for 30 min on ice. The suspension was mixed frequently. The bead-coated cells were immobilized on a magnet and the remaining cells (osteoclast-rich fraction) were decanted into a sterile 50 mL centrifuge tube. Fresh medium was added to the bead-coated cells to dislodge any trapped osteoclasts. This wash process was repeated x10. The bead-coated cells were discarded.

The osteoclasts were enumerated in a counting chamber, using a large-bore disposable plastic pasteur pipette to charge the chamber with the sample. The cells were pelleted by centrifugation and the density of osteoclasts adjusted to 1.5×10^4/mL in EMEM medium, supplemented with 10% fetal calf serum and 1.7g/litre of sodium bicarbonate. 3 mL aliquots of the cell suspension (per treatment) were decanted into 15 mL centrifuge tubes. These cells were pelleted by centrifugation. To each tube 3 mL of the appropriate treatment was added (diluted to 50 uM in the EMEM medium). Also included were appropriate vehicle controls, a positive control (87MEM1 diluted to 100 ug/mL) and an isotype control (IgG2a diluted to 100 ug/mL). The tubes were incubate at 37°C for 30 min.

0.5 mL aliquots of the cells were seeded onto sterile dentine slices in a 48-well plate and incubated at 37°C for 2 h. Each treatment was screened in quadruplicate. The slices were washed in six changes of warm PBS (10 mL / well in a 6-well plate) and then placed into fresh treatment or control and incubated at 37°C for 48 h. The slices were then washed in phosphate buffered saline and fixed in 2% glutaraldehyde (in 0.2M sodium cacodylate) for 5 min., following which they were washed in water and incubated in buffer for 5 min at 37°C. The slices were then washed in cold water and incubated in cold acetate buffer / fast red garnet for 5 min at 4°C. Excess buffer was aspirated, and the slices were air dried following a wash in water.

The TRAP positive osteoclasts were enumerated by bright-field microscopy and were then removed from the surface of the dentine by sonication. Pit volumes were determined using the Nikon/Lasertec ILM21W confocal microscope.

Compounds of this invention are also tested in *in vivo* bone resorption assays standard in the art for evaluating inhibition of bone formation, such as the ovarectomized rat model, described by Wronski *et al.*, *Cells and Materials* **1991**, Sup. 1, 69-74.

General

Nuclear magnetic resonance spectra were recorded at either 250 or 400 MHz using, respectively, a Bruker AM 250 or Bruker AC 400 spectrometer. $CDCl_3$ is deuteriochloroform, DMSO-d_6 is hexadeuteriodimethylsulfoxide, and CD_3OD is tetradeuteriomethanol. Chemical shifts are reported in parts per million (d) downfield from the internal standard tetramethylsilane. Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. *J* indicates the NMR coupling constant measured in Hertz. Continuous wave infrared (IR) spectra were recorded on a Perkin-Elmer 683 infrared spectrometer, and Fourier transform infrared (FTIR) spectra were recorded on a Nicolet Impact 400 D infrared spectrometer. IR and FTIR spectra were recorded in transmission mode, and band positions are reported in inverse wavenumbers (cm^{-1}). Mass spectra were taken on either VG 70 FE, PE Syx API III, or VG ZAB HF instruments, using fast atom bombardment (FAB) or electrospray (ES) ionization techniques. Elemental analyses were obtained using a Perkin-Elmer 240C elemental analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius.

Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Both flash and gravity chromatography were carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel.

Where indicated, certain of the materials were purchased from the Aldrich Chemical Co., Milwaukee, Wisconsin, Chemical Dynamics Corp., South Plainfield, New Jersey, and Advanced Chemtech, Louisville, Kentucky.

In the following synthetic examples, temperature is in degrees Centigrade (°C). Unless otherwise indicated, all of the starting materials were obtained from commercial sources. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. These Examples are given to illustrate the invention, not to limit its scope. Reference is made to the claims for what is reserved to the inventors hereunder.

Example 1

Preparation of Trans-N,N'-bis-(benzyloxycarbonyl-L-leucinyl)-1-3-diamino-cyclopentanone

a) 3-N-phthalimido-cyclopentene

Cyclopent-2-ene-ol (1.05 g, 12.5 mmol) (as described in Brown, H. C.; Hess, H.M. *J. Org. Chem.* **1969**, *34*, 2206) was dissolved in THF (20 ml). Then phthalimide (2.05 g, 14 mmol), triphenyl phosphine (3.675 g, 14 mmol), and diethyl azo dicarboxylate (2.43 g, 14 mmol) were added and the reaction was stirred at RT for 1h. The reaction mixture was concentrated in vacuo, then chromatographed (silica gel, 5% EtOAc/ hexanes) to yield the title compound as a white solid (1.0 g, 37%), ^{1}H NMR (d): 7.81 (m, 2H), 7.69 (m, 2H), 6.09 (m, 1H), 5.62 (m, 1H), 5.38 (m, 1H), 2.81 (m, 1H), 2.45-2.32 (m, 2H), 2.13-2.08 (m, 1H).

b) N-3-cyclopentene-(2-methylene hydroxy)-benzamide

3-N-phthalimido-cyclopentene (1.0 g, 4.7 mmol) was dissolved in isopropanol (12 ml) and water (2 ml). Sodium borohydride was added at 0 degrees C, then warmed to RT. The reaction mixture was diluted with EtOAc (100 ml), then extracted with water, dried with magnesium sulfate, filtered, concentrated in vacuo, and was chromatographed (silica gel, 30% EtOAc/ hexanes) to yield a white solid (0.22 g, 22%), MS(ESI): $M + H^+ = 218$.

c) trans, cis-*N*-(1(3*H*)-isobenzofuranylidene)- 1-bromo-2-hydroxy-cyclopentyl-3-amine

N-3-cyclopentene-(2-methylene hydroxy)-benzamide (0.22 g, 1.0 mmol) was dissolved in chloroform (5 ml) and N-bromosuccinimide (0.2 g, 1.2 mmol) was added at RT and stirred 1h. The solution was diluted with chloroform (100 ml), then was extracted with aqueous $Na_2S_2O_3$-5 H_2O, dried with magnesium sulfate, filtered, concentrated, and chromatographed (silica gel, 25% EtOAc/ hexanes) to yield the title compound as a white solid (0.13 g, 43%), MS(ESI): $M + H^+ = 296$.

d) Cis-*N*-(1(3*H*)-isobenzofuranylidene)- cyclopentene-2-oxide-1-amine

Trans, cis-*N*-(1(3*H*)-isobenzofuranylidene)- 1-bromo-2-hydroxy-cyclopentyl-3-amine (2 g, 6.8 mmol) was dissolved in EtOH (3 ml), then potassium hydroxide was added (0.5 g, 9 mmol) and the reaction was stirred at RT for 3h. The reaction was diluted with water and EtOAc (1:1, 100 ml), and the combined organics were dried, filtered, concentrated, and chromatographed to yield the title compound as an oil which solidified upon standing (1.17 g, 81%), MS(ESI): $M + H^+ = 216$.

e) (+-)-trans-1,3-diamino cyclopentanol

Cis- *N*-(1(3*H*)-isobenzofuranylidene)- cyclopentene-2-oxide-1-amine (0.5 g, 2.3 mmol) was dissolved in EtOH (10 ml) and con. aq. ammonium hydroxide was added (18 ml). The reaction mixture was sealed in a steel bomb and was heated to 100 degrees C for 1 h. The reaction was then cooled to RT and was extracted with methylene chloride, dried, filtered, concentrated, and lyophilized to yield a white solid which was used in the following reaction without further purification (0.25 g, 94%), MS(ESI): $M + H^+ = 117$.

f) Trans-N,N'-bis-(benzyloxycarbonyl-L-leucinyl)-1-3-diamino-cyclopentanol

To a stirring solution of N-Cbz-L-leucine (Bachem) (0.64 g, 2.4 mmol) in 10 mL of DMF was added (+-)-trans-1,3-diamino cyclopentanol (0.14 g, 1.2 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.46 g, 2.4 mmol) and 1-hydroxybenzotriazole (0.324 g, 2.4 mmol). After stirring at room temperature for 3.5 h, the solution was diluted with EtOAc (200 ml), and the combined organics were extracted with water, brine, then dried with magnesium sulfate, filtered, concentrated in vacuo, and chromatographed (silica gel; 80% EtOAc/ hexanes) to yield the title compound as a white solid: (0.18 g, 25%). MS(ESI): $M + H^+ = 611$.

g) Trans-N,N'-bis-(benzyloxycarbonyl-L-leucinyl)-1-3-diamino-cyclopentanone

Trans-N,N'-bis-(benzyloxycarbonyl-L-leucinyl)-1-3-diamino-cyclopentanol (0.17 g, 0.28 mmol) was dissolved in acetone (2 ml). Jones reagent (0.5 ml, 1.5 M) was added added and the reaction was stirred overnight. The excess Jones reagent was then quenched with isopropanol (1 ml) and the reaction was diluted with water (10 ml) and was extracted with EtOAc (2 x 20 ml). The combined organic layers were extracted with water (2 x 20 ml), then brine (20 ml), then were dried with magnesium sulfate, filtered, concentrated in vacuo, and chromatographed (silica gel, 70% EtOAc/ hexanes) to produce a white solid (0.085 g, 50%); MS(ES) $M+H^+= 609$, $M+ Na^+ = 631$.

Example 2

Preparation of trans-N,N'-bis-(benzyloxycarbonyl-L-leucinyl)-1-3-diamino-cyclohexanone

a) Trans-N,N'-bis-(benzyloxycarbonyl-L-leucinyl)-1-3-diamino-cyclopentanol

To a stirring solution of N-Cbz-L-leucine (Bachem) (0.6 g, 2.3 mmol) in 10 mL of DMF was added (+-)-trans-1,3-diamino cyclohexanol (0.14 g, 1.1 mmol) (as described by Sammes, P.G.; Phetford, D. *J. Chem. Soc. Perkin Trans. I*, **1989**, 655), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.44 g, 2.3 mmol) and 1-hydroxybenzotriazole (0.31 g, 2.3 mmol). After stirring at room temperature for 3.5 h, the solution was diluted with EtOAc (200 ml), and the combined organics were extracted with water, brine, then dried with magnesium sulfate, filtered, concentrated in vacuo, and chromatographed (silica gel; 60% EtOAc/ hexanes) to yield the title compound as a white solid: (0.22 g, 32%). MS(ESI): $M + H^+ = 625$, $M + Na^+ = 647$

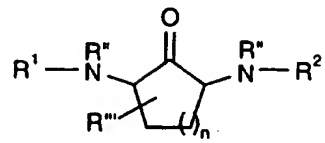
b) Trans-N,N'-bis-(benzyloxycarbonyl-L-leucinyl)-1-3-diamino-cyclopentanone

Trans-N,N'-bis-(benzyloxycarbonyl-L-leucinyl)-1-3-diamino-cyclopentanol (0.22 g, 0.35 mmol) was dissolved in acetone (2 ml). Jones reagent (0.5 ml, 1.5 M) was added added and the reaction was stirred overnight. The excess Jones reagent was then quenched with isopropanol (1 ml) and the reaction was diluted with water (10 ml) and was extracted with EtOAc (2 x 20 ml). The combined organic layers were extracted with water (2 x 20 ml), then brine (20 ml), then were dried with magnesium sulfate, filtered, concentrated in vacuo, and chromatographed (silica gel, 70% EtOAc/ hexanes) to produce a white solid (0.085 g, 40%); $M + H^+ = 623$, $M + Na^+ = 645$.

The above description fully discloses how to make and use the compounds of the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

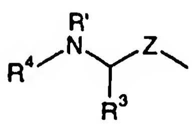
1. A compound according to formula (I):

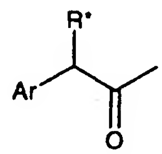


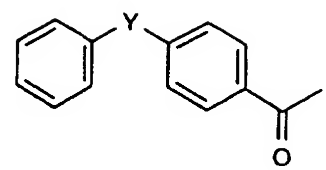
(I)

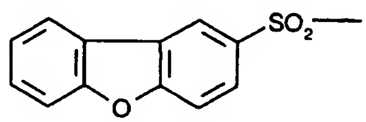
wherein:

R^1 is

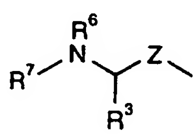
,

,

, or

;

R^2 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^5C(O)$-, $R^5C(S)$-, R^5SO_2-, $R^5OC(O)$-, $R^5R'NC(O)$-, $R^5R'NC(S)$-, adamantyl-C(O)-, or

;

each R" independently is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R"' is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

each R^3 independently is H, C_{2-6}alkenyl, C_{2-6}alkynyl, Het, Ar or C_{1-6}alkyl optionally substituted by OR', SR', NR'_2, $R'NC(O)OR^5$, CO_2R', $CO_2NR'_2$, $N(C=NH)NH_2$, Het or Ar;

R^4 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, $R^5C(O)$-, $R^5C(S)$-; R^5SO_2-, $R^5OC(O)$-, $R^5R'NC(O)$-, $R^5R'NC(S)$-, R'HNCH(R')C(O)-, or $R^5OC(O)NR'CH(R')C(O)$-;

each R^5 independently is C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, Ar-C_{0-6}alkoxy, Het-C_{0-6}alkoxy, or C_{1-6}alkyl optionally substituted by OR', SR', NR'_2, $R'NC(O)OR^5$, CO_2R', $CO_2NR'_2$, $N(C=NH)NH_2$, Het or Ar;

R^6 is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl and R^7 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, Het-C_{0-6}alkyl, R^5C(O)-, R^5C(S)-, R^5SO_2-, R^5OC(O)-, R^5R'NC(O)-, R^5R'NC(S)-, R'HNCH(R')C(O)-, or R^5OC(O)NR'CH(R')C(O)-; or R^6 and R^7 are connected to form a pyrrolidine, a piperidine, or a morpholine ring;

each R' independently is H, C_{1-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

R* is H, C_{1-6}alkyl, C_{3-6}cycloalkyl-C_{0-6}alkyl, Ar-C_{0-6}alkyl, or Het-C_{0-6}alkyl;

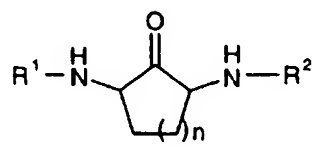
Y is a single bond or O;

each Z independently is CO or CH_2; and

n is 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.

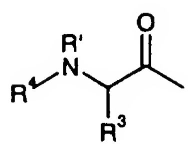
2. A compound according to formula (Ia):



(Ia)

wherein:

R^1 is



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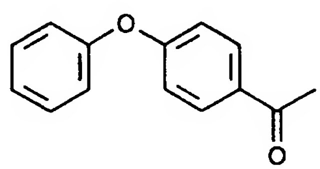

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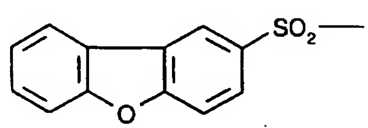
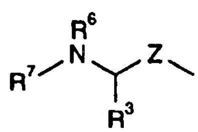
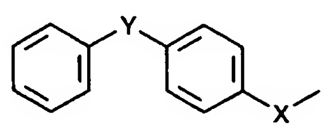


;

R^2 is



or



;

X is CO, SO_2, or CH_2-CO;

Y is a single bond or O;

Z is CO or CH_2;

each R^3 independently is C_{4-6}alkyl, C_{4-6}alkenyl, or benzyl;

R^4 is C_{1-6}alkyl, Ar-C_{0-6}alkyl, R^5CO-, R^5SO_2- R^5OC(O)-, or R^5NHCO;

R' is H or C_{1-4}alkyl;

R^6 is H or C_{1-4}alkyl;

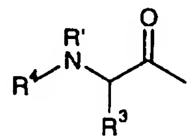
R^7 is C_{1-6}alkyl, Ar-C_{0-6}alkyl, R^5CO-, R^5SO_2- $R^5OC(O)$-, or R^5NHCO;

each R^5 independently is Ar-C_{0-6}alkyl or Het-C_{0-6}alkyl; and

n is 1 or 2;

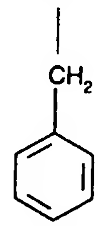
or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 2 wherein R^1 is



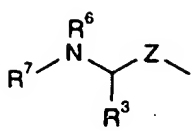
4. A compound according to claim 3 wherein R^4 is $R^5OC(O)$-.

5. A compound according to claim 4 wherein R^5 is



6. A compound according to claim 3 wherein R' is H and R^3 is i-butyl.

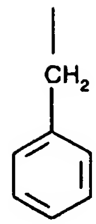
7. A compound according to claim 1 wherein R^2 is



, in which Z is CO.

8. A compound according to claim 7 wherein R^7 is $R^5OC(O)$-.

9. A compound according to claim 8 wherein R^5 is



10. A compound according to claim 7 wherein R^6 is H and R^3 is i-butyl.

11. A compound according to claim 1 which is:
trans-N,N'-bis-(benzyloxycarbonyl-L-leucinyl)-1-3-diamino-cyclopentanone; or
trans-N,N'-bis-(benzyloxycarbonyl-L-leucinyl)-1-3-diamino-cyclohexanone;
or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

13. A method of inhibiting a cysteine protease which comprises administering a compound according to claim 1.

14. A method according to claim 13 wherein the cysteine protease is cathepsin K.

15. A method of inhibiting bone loss which comprises administering a compound according to claim 1.

16. A method of treating osteoporosis which comprises administering a compound according to claim 1.

17. A method of treating gingival or peridontal disease which comprises administering a compound according to claim 1.

18. A method of treating a disease characterized by excessive cartilage or matrix degradation which comprises administering a compound according to claim 1.

19. A method according to claim 18 wherein said disease is osteoarthritis or rheumatoid arthritis.

20. A compound according to any one of claims 1 to 11 for use as a medicament.

21. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of diseases in which inhibition of a cysteine protease is a factor.

22. The use of a compound according to claim 21 wherein the cysteine protease is cathepsin K.

23. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the inhibition of bone loss.

24. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of osteoporosis.

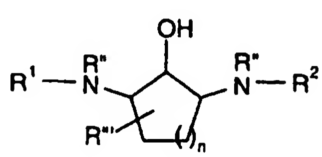
25. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of gingival or peridontal disease.

26. The use of a compound of the formula (I) as defined in claim 1 in the manufacture of a medicament for the treatment of diseases characterized by excessive cartilage or matrix degradation.

27. The use of a compound according to claim 26 wherein the disease characterized by excessive cartilage or matrix degradation is osteoarthritis or rheumatoid arthritis.

28. A process for preparing a compound of the formula (I) as defined in claim 1, which process comprises:

reacting a compound of the formual (II):



(II)

wherein R^1, R^2, R", R''' and n are as defined in formula (I), with any reactive functional groups protected, with an oxidizing agent;
and thereafter removing any protecting groups and optionally forming a pharmaceutically acceptable salt.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/15029

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07C 211/00; A61K 31/13
US CL :564/461, 462; 514/ 579, 825, 900
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 564/461, 462; 514/ 579, 825, 900

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, E	US 5,668,128 A (TSUBOTANI et al) 16 September 1997, col. 1 lines 10-32; col. 27 lines 12-30.	1-28

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search: 22 SEPTEMBER 1997

Date of mailing of the international search report: 29 OCT 1997

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